clinical trial.

Next slide, please.

If one looks at the clinical success at the end of therapy window, the same pattern of success up to and including those isolates in the amoxi.-clav. MIC of four -- next slide, please -- then we see the same even at the test of cure window.

Next slide.

Kind of a summary slide to look at the summary of high clinical and bacteriologic response rates in those isolates of amoxi.-clav. MIC of four. One notes a slightly decreased rate of eight, again, following the model.

Next slide, please.

Conclusions for amoxi.-clav. MIC of four. The clinical trial data support the efficacy of Augmentin ES against Streptococcus pneumoniae with amoxi.-clav. MICs up to and including four micrograms per milliliter. The less efficacy was noted in amoxi.-clav. MICs of eight.

These results are consistent with predictions for the PK/PD models in animal studies performed before trial.

Next slide.

The product we're discussing is Augmentin,

and one of the beauties is its beta-lactamase inhibiting abilities. We looked at the beta-lactamase producing organisms, and what we saw here is continued, strong, bacteriologic success followed with clinical success at the end of therapy window, and those beta-lactamase producing organisms, Haemophilus influenzae and Moraxella catarrhalis.

Thirty-seven percent of our Haemophilus for beta-lactamase producing 100 percent of our Moraxella for beta-lactamase producing organisms. The other interesting thing on this slide, I feel, is that the 87 and 85 percent clinical success at end of therapy, while in the range of those suggested by the IDSA guidelines are similar to the 83 percent end of therapy clinical success rate in those patients with penicillin resistant Streptococcus pneumoniae.

Next slide.

Safety. Had an overall excellent safety profile. It was similar to that of the currently marketed formulation in the head-to-head trial, 447, as discussed earlier. It builds on 20-plus years, European, 16-plus years in the United States, experience with the use of Augmentin in the treatment of infections in children.

Conclusions. We feel that the Augmentin

ES clinical trial has demonstrated excellent clinical and bacteriologic efficacy in children with acute otitis media caused by the key pathogens including penicillin resistant Streptococcus pneumoniae.

The PK/PD study, 574, with a 46 percent time of MIC -- an MIC of four, in vivo animal studies and the clinical data, all support efficacy against isolates of Streptococcus pneumoniae with amoxi.-clav. MICs up to and including four micrograms per milliliter.

It maintains excellent clinical and bacteriologic efficacy in those very common beta-lactamase producing organisms that are common in respiratory tract infections, including otitis media.

Finally, it maintains the safety profile of currently marketed formulation.

And with that I'll take deep breath, and thank you for your time.

I'll also introduce Dr. McCracken who will discuss the role of Augmentin ES in treating acute otitis media today.

Thank you.

DR. McCRACKEN: Good morning, and I appreciate the opportunity to address the committee, and I'd first like to start with a disclosure

statement.

GlaxoSmithKline has paid for my expenses to attend the meeting. I am advisor to GlaxoSmithKline for ne product development, as I am for at least a half a dozen other pharmaceutical companies.

I have no current studies, although I've been supported in the past by GlaxoSmithKline for research.

I do not own stock in GlaxoSmithKline, and I stand to gain nothing from the decision made by this committee.

Now, the following are my comments, my opinions only about this drug and about other drugs for management of acute otitis media, and it's based on an experience of more than 30 years in pediatric infectious disease. I hate to admit that, and from the knowledge of the data on Augmentin in the 90 milligram per kilogram formulation, as well as with other drugs.

There are no slides. This is purely opinion statements I'm making, and I'm going to address just four issues.

The first, what should be the standard for development and evaluation of antimicrobials for the

treatment of acute otitis media.

Well, first, and it's clearly demonstrated by Bill Craig, I believe pharmacokinetic and pharmacodynamic studies must be done, and I want to make one comment about study 446 that will be addressed later by the FDA. This is a study done by myself.

There are limitations to that study, and it should be realized at the outset. First, it's measuring serum in middle ear fluid concentrations after the first dose of antibiotic only, before the steady state, which for middle ear fluid concentrations where the half-life is longer than it is in the plasma, cumulation may have occurred.

And the second limitation is that only the first three hours were evaluated, and for middle ear fluid concentrations, we saw the trend going up. So perhaps the peak was not seen until four to five hours.

Despite that, 12 of the 14 samples in middle ear fluid had concentrations greater than two micrograms per mL.

With regard to pharmacodynamics, I think Dr. Craig has clearly shown the correlations for otitis media, but I'd like to tell you about an

analogous situation in which I feel I have the expertise, and that is in bacterial meningitis using the rabbit meningitis model where we have clearly shown that the pharmacodynamics of an antibiotic in the rabbit model predict accurately. The dosage, frequency of administration, and rate of bacteriologic cure that will be seen in infants and children with the same disease, pneumococcus or Haemophilus meningitis.

Most recently we demonstrated that using trovafloxacin where we completed a large study worldwide, predicting the dosage, frequency of administration, and concentrations in spinal fluid which were verified, and the rate of bacteriologic sure in spinal fluid based on these pharmacodynamic principles was predictably above 95 percent, and indeed, in the infants and children, it was 98 percent.

So I feel very strongly that pharmacodynamics, when done properly, are very predictive.

Now, should it be a single or double tap study? Ideally double tap because it's the only objective measure you have.

Some of you on the committee, Dr. Wald

right in front of me, are very versed pediatricians who know the difficulty in diagnosing acute otitis media, especially in the young infant with recurrent disease who is seen at two, three, four, five weeks after an acute episode, who has fluid and a concomitant viral infection.

That's a tough call to say that that's AOM or OME with a concomitant viral infection. That's very subjective in many instances.

Whereas a double tap study gives you objective data, and a double tap study allows you to verify the pharmacodynamic predictions, which Dr. Craig has addressed nicely; to determine bacteriologic effectiveness; and to assess clinical success vis-a-vis the bacteriologic response, and a clear correlation has been show, and Dr. Marchant indicated, not only from his study, in the study in the Pediatric Infectious Disease Journal in 1998, the September issue by Dr. Dagan, but even more recently a third confirmation study in the February 2000 issue of the Pediatric Infectious Disease Journal.

One other point about studies. I feel very firmly that any new drug, orally administered drug, to be studied in pediatrics must evaluate the effectiveness of that drug or its effect, I should

say, on the nasopharyngeal flora.

We are in an era of resistance, and we know that antimicrobials given frequently have an effect on the oral bacterial flora, and this is very critical to evaluate.

The second point I wish to raise, in a double tap study, when is the best time for the second tap?

Now, as you've heard clearly shown by Colin, three to five, four to six days has been the standard since 1960. Who's about to change that? And what are you going to change it to?

You're going to want to do a tap later. Well, any of you who deal with children know that when they get to be seven, eight, nine days, they're feeling pretty good, and they're not going to want a tap, the mother or the patient, and you have a much higher incidence of a dry tap.

Well, does antibiotic suppression render the results less meaningful? I don't think so, and let me give you an analogous situation: bacterial meningitis.

In the early '80s, we did a study of Haemophilus influenzae Type B meningitis. That was a common cause in those days, and we looked at the

spinal fluid culture at 18 to 30 hours after initiation of therapy, and we could clearly show that when that culture was positive, which it was in 22 percent of the patients with Haemophilus meningitis, outcome was worse as judged by neurologic and audiologic assessments at follow-up examinations.

And this was significantly different than the children who had sterile spinal fluids at that second tap, and we know in those spinal fluids, because we measured it because we were using ceftriaxone at the time mainly, that there was a lot of drug there.

And yet despite that a positive culture had a very significant correlation without them.

The third point I wish to address, why is the end of therapy a more realistic endpoint for assessing clinical success? Well, I think that's been reviewed very nicely by Colin.

At the time of cure evaluation, or 25 to 30 days, there are only ten to 15 percent that are relapse with the same organism. The rest are either sterile or reinfection with a new organism.

Now, what was the intent in the 1992 IDSA FDA guidelines? Well, the principal author of those guidelines, Dr. Jerome Klein, has told me as of

Saturday, last Saturday when I had an hour conversation with him at home, that the test of cure was not intended to be the evaluation of the efficacy of the drug for the acute episode, but rather the evaluation for the presence of fluid.

It was thought then, as it is now, that fluid, one, predisposes to recurrent disease, but, two, and more importantly, may have the adverse effect of decreasing hearing and perhaps having an effect on language skill development.

Also, it was hoped -- it turned out to be a false hope, I believe -- that certain antibiotics might have a beneficial effect on fluid. That is being more active like ceftriaxone, or having anti-inflammatory properties as the macrolides do, but so far that has not been realized.

It must be remembered that in the particular study that's being discussed that the very patients that everyone wants to know about are those at the highest risk of recurrent disease. They're young. They've had recurrent episodes of acute otitis media. They've had repeated courses of antibiotics. They're in day care, and it's the winter full of viral infections.

So, therefore, the further you go out, the

more likely there is going to be difficulty in interpreting what is a clinical success or failure.

Now, finally, in my opinion, the following are the reasons why the larger dosage formulation of Augmentin is the most appropriate therapy in patients who either fail acute otitis media, have recurrent acute otitis media, or at high risk for disease by resistant pathogens for any reason.

One, as shown just by Brian Wynne, that with MICs of four to eight through amoxicillin with the Strep. pneumoniae, bacterial eradication at the second tap occurred in 80 percent per protocol and 77 percent by ITT, which the MICs are four to eight.

Clinical success at end of therapy, 82 percent per protocol and 70 percent by IDT, and that 70 percent fall-off is due to the strains with MICs of eight.

The larger dosage formulation is very effective for treatment of Haemophilus caused by beta-lactamase negative and positive strains,a nd there is no other oral formulation antibiotic presently available to pediatricians that can make the claim that they're effective against penicillin resistant Strep. pneumo. and beta-lactamase positive Haemophilus. No other.

I'd like to remind you that there's actually a track record with this combination drug, that is, amox. plus amox.-clav. Many of us have recommended for years that amox. be poured into amox.-clav. to get to a formulation of around 80 or 90 milligrams per kilogram.

Indeed, the FDA or the CDC in the panel of expert consensus statement, published in January of 1999 in the Pediatric Infectious Disease Journal, recommended the higher dosage. That's January 1999.

Recently I was lecturing at a meeting in Dallas of 180 pediatricians, and I asked them for a showing of hands of how many used amox. plus amox.-clav. to bring up the higher dosage, and clearly three quarters of them raised their hands.

So finally, safe, well tolerated and effective antibiotic alternatives to the larger dosage formulation of amox.-clav. do not exist. There are 17 approved antibiotics with an indication for treatment of acute otitis media. One of those is intramuscular, and that's obviously ceftriaxone.

So with the 16 orally administered antibiotics with an indication, only the 90 milligram per kilogram amox.-clav. formulation is effective against the two most frequent resistant pathogens

causing disease in these high risk infants and children.

Again, let me thank you for allowing me to address the committee.

CHAIRMAN RELLER: It's 10:30. We'll now have our break and reconvene at 10:45 for a discussion of the material already presented.

MR. PEREZ: One quick announcement. Would C.N. Graham, if they're present, please see Nancy at the table outside?

Thank you.

(Whereupon, the foregoing matter went off the record at 10:32 a.m. and went back on the record at 10:50 a.m.)

CHAIRMAN RELLER: I should like to ask everyone to return to their seats so that we can begin the discussion of this morning's presentations.

This morning we had multiple presentations that emphasized the critical issues of trial design and then the sponsor and their consultants presented pharmacokinetic/pharmacodynamic data, as well as clinical results information.

These issues are open for discussion. Questions for the presenters from panel members? Dr. Archer.

DR. ARCHER: I have a question for the sponsor about the test of cure clinical failures. Are there any bacteriological data on those patients? Were any of them, and if so, how many of them, had tympanocentesis done at the test of cure date? And what were the criteria for clinical failure at test of cure?

DR. WYNNE: Yes. Essentially, no, as our primary population was Streptococcus pneumoniae, and they had already had two tympanocenteses. There were a total of three patients who had Streptococcus pneumoniae isolated on any third tympanocentesis at one site who went that far in the window after end of therapy and before test of cure, actually days 21 and 22, and they grew Streptococcus pneumoniae again at days 21 and 22. Evidence will show that that reinfection, self-inoculation.

DR. ARCHER: That didn't really answer my question. Of those patients, and if you look at the percentages, there were 30-some of the patients who had -- or more. How many of those actually had a tympanocentesis who were clinical failures at test of cure, day 21? And of those, how many had any bacteria? How many had Strep. pneumo.? How many of those were penicillin resistant?

DR. WYNNE: The answer is that three --

DR. ARCHER: Total of three?

DR. WYNNE: -- a total of three had penicillin resistant Streptococcus pneumoniae, and at repeat tap at test of cure window, and they grew penicillin resistant. Three recurrences.

DR. ARCHER: So there were only three taps done?

DR. WYNNE: Well, there was some Haemophilus influenzae, too, but three Streptococcus pneumoniae. There were six of those, well, because remember the Haemophilus population. Not all of them had a mandated repeat tap.

DR. ARCHER: I understand. I just want to know how many actually had a tap at that 21 day, at the test of cure day.

DR. WYNNE: A total of three Haemophilus and three Streptococcus pneumoniae.

DR. ARCHER: Oh, three who started off with Haemophilus and three who started off with --

DR. WYNNE: Right, with Streptococcus pneumoniae.

DR. ARCHER: Okay. Out of?

DR. WYNNE: Six out of --

DR. ARCHER: Okay.

DR. WYNNE: -- 383 bacteriologic confirmed cases.

DR. ARCHER: No, no.

DR. WYNNE: At entrance.

DR. ARCHER: Out of the clinical failures.

DR. WYNNE: Well, out of anything, yes. They were all tapped because they were clinical failures. No one was tapped at that window for success.

DR. ARCHER: Right, okay. So only six of the clinical failures had a tympanocentesis. Is that what I understand?

DR. WYNNE: Yes.

DR. ARCHER: And they all grew bacteria?

DR. WYNNE: Yes.

DR. ARCHER: And none of them were penicillin resistant?

DR. WYNNE: No, those who were penicillin resistant remained penicillin resistant.

DR. ARCHER: So were they relapses? Were they typed?

DR. WYNNE: They were typed, and it was three. And of those three, much like the literature, it shows about a 40 percent new infection. We had a 33; one out of three was a different serotype. Two of

those were the same serotype, which does not necessarily mean it was a relapse because kids go back to day care and are exposed to the same serotypes of a nasopharyngeal colonization.

But, yes, one was completely different. Two were the same.

DR. ARCHER: Okay. What were the criteria for clinical failure?

DR. WYNNE: Criteria for clinical failure were, as determined by the investigator, at any time point in the regular scheduled visit or during the course of the therapy if the parent felt the child was worsening or not clinically improving. They were to be brought back to the investigator within 24 hours, and then it was based on clinical signs and symptoms as determined by the investigator, and there was a whole -- well, would you like to see a slide of the criteria?

DR. ARCHER: I just wanted to know was the clinical failure criteria the same as the entry into the study criteria.

DR. WYNNE: Yes.

DR. ARCHER: Did it require the bulging drum and the whole bit?

DR. WYNNE: Yes.

DR. ARCHER: Okay.

DR. WYNNE: Right.

CHAIRMAN RELLER: Dr. Besser.

DR. BESSER: Did you look at risk factors for failure? You presented some data on risk factors for carriage of penicillin resistant Strep. pneumo., but did you analyze your data to see if those risk factors were also predictive of failure at the test of sure visit?

DR. WYNNE: Yes, we did do that analysis, and what we found was that the PRSP subset of failures were more likely -- again, you're talking in failures at that end of therapy window and on of an n of ten. Of that n of ten, there was a higher rate of history of otitis media, and they were younger.

DR. BESSER: I was asking about your overall clinical failures, not just your PRSP subset. In terms of your clinical failures at test of cure, did you see that those were younger, younger patients and had the similar risk factors that are known for relapse or infection?

DR. WYNNE: Yes. Analysis indicated that risk factors, if you coded them in a system of giving a point for a risk factor and not a point for not, so zero or one each time, those who had two or fewer risk

factors were more likely to be clinical successes than those who had three or more regardless of baseline pathogen, Strep. pneumoniae not done for the other populations.

CHAIRMAN RELLER: Dr. Soreth.

DR. SORETH: Dr. Reller, we have a back-up slide that we prepared with regard to repeat tympanocentesis for those children, the subset of children who were clinical failures who had either a second or a third tap beyond the on therapy tap, which we can show if that's of help to the committee, getting back to Dr. Archer's question.

DR. MAKHENE: Good morning. I'm Dr. Makhene. I'm the medical review for the FDA team, and I haven't done my presentation yet, but we'll go through some of the back-up slides that I prepared just looking at the failures to hopefully try to answer some questions that you may have and specifically try to address the question that Dr. Archer raised.

I went through essentially the information that had been provided specifically from Dr. Jacob's lab looking at when patients had repeat taps and what those results were, and essentially Dr. Archer's question goes to taps beyond the on therapy visit,

which is day four to six.

In reviewing that information that was provided by the sponsor, what I found was that there were 25 patients who had positive taps beyond day four to six essentially at the time of clinical failure.

Of those, there were 18 patients who had -- and what I did was I broke out the isolates and looked at who had what isolate at baseline and at the time that the tap was actually repeated.

There were 18 patients in the 25 who had taps beyond the on therapy visit, who had H. influenzae at baseline and on the repeat tap. In five of those -- sorry. That was at the four to six visit.

However, what I saw was that in looking again at what the organism was at baseline compared to what it was at the time that the patient was retapped, a third were beta-lactamase positive pairs, and about 56 were beta-lactamase negative pairs, and three of the patients had discordant either beta-lactamase at the beginning, which became beta-lactamase negative, which became beta-lactamase positive, and in one case it was actually the reverse.

There were several patients who had mixed pathogens, and so I've not really included a summary of those. One patient had Staph. aureus at baseline

and also at the repeat tap.

There were three patients in whom they had PRSP at baseline, but at the time that the tap was repeated on failure either at visit four or visit three, as it was documented in that information grew PRSP on the repeat tap, and overall there were five patients from baseline who had repeat taps that show PRSP at both time points.

And just go to the next slide, John.

So what I've done is just essentially summarize first the patients who were bacteriologic failures for PRSP. There were five of those out of the total 41 in the PRSP ITT population with the information at baseline and at repeat, and as Dr. Wynne said, there were three patients who had a positive tap beyond the on therapy visit.

The dates or the study day that were documented were day 14, day 15, and day 22, which is a little bit different from, I guess, the days that he's told you about, but essentially I agree that there were three patients beyond the on therapy visit who essentially had PRSP at baseline, and then also had it at the time that they failed.

And in looking at those three patients -- you can go to the next slide, John -- of those three

patients that are summarized here that were clinical failures and had a repeat tap, you can see the first, second, and the last patient are the ones that make up that subset of patients who had a tap at the time of failure and were also clinical failures beyond that time.

And that's it. I don't know if that helps you in terms of trying to answer some of your questions. Okay?

Thanks. Thanks, John.

CHAIRMAN RELLER: Dr. Giebink.

DR. GIEBINK: Could I ask a related question on this slide perhaps before you sit down? Is there either serotype or clonal data on these pairs of PRSP?

DR. MAKHENE: I know Dr. Wynne mentioned that there were some information that was available to them. There was nothing that was available to us in terms of what was submitted to the FDA to review. I'm not sure whether it is referring to these particular patients.

I guess I'd have to let the sponsor speak to that.

DR. WYNNE: The quick answer was what was mentioned earlier. One of those three had a different

serotype. So 33 percent of an n of three, I'm not sure that's overwhelmingly helpful, but literature sources, patients with third tympanocentesis, three repeat tympanocentesis performed in the test of cure window, two patients with Streptococcus pneumoniae baseline, one on day 21, two on day 22.

Pulse electrophoresis differentiated between the organisms, a different strain, 33 percent, which is kind of a hard percentage with an n of three.

Nonetheless, we felt in support of the data of Dr. Carlin and Dr. Leibowitz showing that recurrences after the end of therapy window were, with an n of three, as likely to be reinfection as a relapse.

CHAIRMAN RELLER: Dr. Harrison.

DR. HARRISON: Two questions. One, do we know the MIC on those three? Are those MICs of four, eight, 16?

DR. MAKHENE: For the three failures? Yeah, we do, and I have to just quickly look and I can tell you if you can hold for a second.

DR. HARRISON: While you're looking at that, if I heard it right, you had different days for those taps than it appears that Brian -- did I get the wrong --

DR. MAKHENE: No, what I have done is just essentially looked at the information that was given to me in terms of the three failures that I found and saw at the time that they were actually declared failures and the information that corresponded with that.

DR. HARRISON: So are your days from the days of onset of therapy or from the day -- I mean, these are days after --

DR. MAKHENE: It's with respect to the day of study entry.

DR. HARRISON: Okay. So how do we resolve that discrepancy? At least to me it seemed like there was a discrepancy there. You had some -- you didn't have any as far out as 22, and it sounded like from the slide I saw that they were off.

DR. MAKHENE: Right, and in looking, I recognized that they were in going through the briefing packet, but all I had was, you know, the information that was submitted and had to just go based on that. If they were --

DR. WYNNE: I think the disconnect becomes a matter of we had two isolates from one of the patients. We looked at them as isolates, what happened if you eradicate two from each year, and so

what Dr. Makhene is looking at, we had included the day 14. It was actually that patient's end of therapy visit, and they were declared a failure at that time. They weren't considered. So they were already a failure.

They aren't patients who are considered a relapse. You're a patient we considered not -- our primary clinical time point was end of therapy. When they came in for that evaluation, they still had clinical signs and symptoms under tympanocentesis and were a failure.

That could be the disconnect.

CHAIRMAN RELLER: Dr. Giebink.

DR. GIEBINK: One important factor that relates strongly to clinical outcome is laterality of disease, and I didn't hear this morning at all in any of the presentations the prevalence of disease laterality. How many of these cases were bilateral and how many were unilateral, and was there a change in that balance at either the end of therapy or the test of cure time point?

DR. COCCHETTO: Dr. Giebink, we'll take that question away with us during the break and see if we can pull that from our records.

CHAIRMAN RELLER: Dr. Leggett.

DR. LEGGETT: A couple of questions just getting back to the MIC issue. Could you tell us were the MICs different? Did they increase from the baseline to the failure for both H. flu. and the pneumococcus?

And then the second question for the sponsor: did someone do an analysis of the median kinetics rather than the mean kinetics?

DR. COCCHETTO: Yes. Let me ask Dr. Jacobs to address that.

DR. JACOBS: The question that I'm addressing is did the MICs of second or subsequent tap isolates change from baseline isolates of the same patient, and the answer is, no, with the exception of a few patients where there was a different organism, but clearly the MIC changed.

But we did a pulse field electrophoresis and serotapping of all the Strep. pneumos., and where the pulse field and the serotype were the same, the MIC had not changed, but again, beyond day ten of treatment, there were only three such isolates.

CHAIRMAN RELLER: Dr. Makhene.

DR. MAKHENE: To answer your question, Dr. Harrison, John, could you put up slide 58?

For the first patient the MIC was four,

and this was at baseline, and for the second patient the MIC was two, and for the last patient from whom the isolate was found at day 22, the MIC was four.

DR. MURRAY: Just a comment, and then a question.

The comment is that I'm not sure it's actually totally relevant to site studies from the '80s looking at relapse when all of the organisms were penicillin susceptible at that time, and I mean, it's important, but it doesn't necessarily imply that the same thing will hold for a penicillin more resistant organism.

So I was a little troubled that those were making perhaps not valid comparisons,b ut my real question, and it may be in part addressed by the FDA, it sounds like the sponsor had one endpoint, which was bacterial.

Could I just be reviewed on the primary endpoints going into the study from the sponsor's point of view?

I thought it was bacteriologic, and then it sounds like FDA used a different primary endpoint, and I was wondering how did that evolve in the discussions, and we're left with three sets of endpoints: bacteriologic, end of therapy, and test of

cure, and which ones were the primary ones going into the study?

CHAIRMAN RELLER: Dr. Makhene.

DR. MAKHENE: Okay. Thanks, Dr. Reller.

The primary endpoint as you've alluded to for the sponsor was the bacteriologic response at the on therapy visit, and based on our guidances and the way we typically reviewed acute otitis media trials for the FDA, this endpoint was the bacteriologic response presumed from the clinical response at the test of cure visit.

This point was made to the sponsor in my written review of comments from the written review that were communicated to the sponsor in terms of that, the outcome, the primary outcome being based on bacteriologic response would be presumed from the clinical response at the test of cure.

DR. MURRAY: But that was prior to the study actually being done?

DR. MAKHENE: Yes.

DR. MURRAY: And neither group was using the test of cure at -- sorry -- the clinical response at the end of therapy window?

DR. MAKHENE: Neither group was using it as the primary for the assessment in the bacteriologic

study, but it is a secondary endpoint, and again, there's a difference in terms of making that assessment of whether that final outcome is made at the end of therapy, which is the time unit the sponsor is using versus the test of cure, which is what's used in the FDA analysis.

DR. MURRAY: Okay.

DR. MAKHENE: But we do both acknowledge it as an important endpoint to be measured.

DR. MURRAY: So just so that I understand how the process is, so basically you went into the study with slightly different opinions on what should be the primary endpoint for evaluation?

DR. MAKHENE: Correct.

CHAIRMAN RELLER: Dr. Archer.

DR. ARCHER: I noticed in Dr. Giebink's -- one of his slides, that there's a large disparity between the susceptibility of the resistant penicillin to amox. versus amox.-clav. Does clavulanic acid have any activity -- this is for the sponsor, I guess -- on pneumococci by itself? Does it bind PDPs enough that it provides bacterial activity?

DR. POUPARD: Jim Poupard, a microbiologist from GSK.

In our experience, and I think also we

have two experts here that Michael Jacobs might want to address this issue; in our experience we rarely see a difference between amox. and amox.-clav., and most of the times it's a testing problem.

I think in the case that was presented, it might be related to using different methods at different times. When they're tested at the same time in the same lab, you get very good correlation with some exceptions, but the exceptions are both ways, sometimes higher, sometimes lower.

I don't know if Michael Jacobs wants to also comment on that.

DR. JACOBS: In the testing that I've done, I'm going to give you one example, which was published in antimicrobial agents in chemotherapy Volume 43, page 1905, published in 1999. The figures I got were at the breakpoint of .5 micrograms per mL; 63.5 percent of strains were susceptible to amoxicillin; and 65.8 percent, so about a two percent difference; and at a breakpoint of two micrograms per mL those figures were 93.5 versus 93.9, or .4 percent difference.

And at every MIC throughout the MIC range, the figures were always within a couple of percent of each other, and Dr. Giebink, in fact, asked me why the

figures that he had were different, and without going back to the source material, I'm not sure, but I suspect they used different break points for amox.-clav. because they were published breakpoints for amox.-clav., whereas they weren't for amox. at that time.

CHAIRMAN RELLER: Dr. Leggett.

DR. LEGGETT: Back to my question about the kinetics. The reason I bring this up is when I looked at the very few points that were shown to us, there seemed to be lots of variability. So what I would like to know, since we're right on the cusp, with the mean concentrations of 41 percent for these MIC values, it looked to me that there were at least a couple of kids who were below that and are the failures right at that cusp of two or four or eight that could be explained by drug kinetics.

So I'd like to have a better elucidation of the pharmacokinetic variability. Have Monte Carlo simulations been done, population kinetics been done with all of the 30 years of amoxicillin that's been around?

DR. CRAIG: I can comment specifically on some data that was not submitted to the FDA until December so that they obviously haven't had a

sufficient time to do it.

But this is looking at the individual patients, those 18 patients, and looking at their serum levels individually to see what percentage of them would be above the MIC.

And if one can pull that slide up, which is my very last slide, this is the percentages that one finds for those 18 children. Looking at 35 percent above the MIC, 40 percent above the MIC, and then if anyone really wanted to stretch it out to 50 percent, 17 of the 18 or 94 percent would have it for a MIC of two.

Whether you used 35 or 40 percent, when you get up to four, one would expect the percentage to be somewhere between 80 and 94, and then again when it gets down to the MIC of eight, it clearly falls off.

So I hope this at least answers you. This is with the actual formulation that was used, but again, we didn't present it at the beginning because, as I say, the FDA had not had time to look at all of this data.

CHAIRMAN RELLER: Dr. Roldvold.

DR. ROLDVOLD: Bill, can I ask you a follow-up question on that? Is that total drug concentration or is that unbound drug concentration?

DR. CRAIG: That is total drug concentrations, and with protein binding with amoxicillin of ten to 15 percent, it will change very little.

CHAIRMAN RELLER: Yes, Dr. Christie, you had a question earlier.

DR. CHRISTIE-SAMUELS: Yes, I still do.

Concerning the study design, in patients with bilateral disease were both tympanic membranes tapped or just one? I wasn't clear on that.

DR. MAKHENE: The study was designed with taps being done just in the more symptomatic ear, and that was a study design that we did agree to when the protocol was reviewed.

However, as I said, that's the way the study was designed, but in one of the studies, in one of the sites, actually the investigator did actually tap both ears when he felt that that was appropriate, if there was a bilateral otitis.

DR. CHRISTIE-SAMUELS: Thank you.

CHAIRMAN RELLER: When both ears were tapped, same organism? Same MIC?

DR. MAKHENE: That's tricky. Sometimes, not always, and sometimes in terms of the response, not always the same.

If you'd like to look at that information, I have a slide on that also.

CHAIRMAN RELLER: Do you want to do that now or later?

DR. MAKHENE: It was not part of my presentation. It was a back-up slide. So that's up to you.

CHAIRMAN RELLER: Let's see it now.

DR. MAKHENE: Okay. Slide 60.

And I didn't look at -- just because, you know, there was so much variability, I looked specifically at patients with PRSP, and there were two patients who had discordant taps at baseline in that they had susceptible organism, susceptible strain of Strep. pneumo. in one ear and a resistant strain in the other ear.

And in the first patient, that patient was declared a failure both clinically and bacteriologically at the test of cure visit. However, that patient did not have PRSP shown on the tap.

I need to just go back and mention that in that site where the investigator chose just one ear to report, the right ear was the one that was chosen consistently where he tapped both ears. So the first patient -- actually both patients were considered in

the non-PRSP population, even though they had a pen. resistant strain in the left ear.

So, again, to go to the outcome for the first patient, there was no growth on that tap. However, when the patient was retapped at the time that he failed, H. flu. grew out in that tap.

The second patient, again, with the same isolates at baseline, pen. susceptible strain in the right ear, pen. resistant strain in the left ear, was withdrawn from the study and had a repeat tap done at some later point, and that tap grew PRSP in both ears, and the patient was withdrawn for diarrhea on day six, so was not included in the analysis.

CHAIRMAN RELLER: Thank you.

Dr. Ebert and then Dr. Archer.

DR. EBERT: There's a follow-up question more specifically addressing the issue of the pharmacokinetics in middle ear fluid. I'm assuming that the assays were done by a chromatographic or other assay, chemical assay. Is there data which has looked at the biologic activity of antimicrobials and specifically amoxicillin in middle ear fluid?

I'm particularly interested in patients who had concomitant infections with beta-lactamase producing strains.

DR. McCRACKEN: The study 446 that we did was a biologic assay. We did not -- because of the amount of fluid, there were no cultures performed on those because we wanted all of the fluid for measurement of both amox. and clavulanate. So we could not do cultures at the same time. So I don't know if they were beta-lactamase producing strains there.

DR. HARRISON: I have a comment about that if you would like to hear more about that.

There was a study by Dr. Book where he looked at middle ear fluid and did cultures and did biologic assays looking for the concentrations and found that in the face of beta-lactamase producing organisms, that there was less amoxicillin. In fact, it was undetectable in I think about 18 percent of the cases, but less than you would have predicted from serum concentrations, and that it actually predicted failure in his.

It was not -- you know, as most of these are, this isn't hundreds of patients. This is about two dozen patients, and we also did a study looking at the biologic activity in a small number of patients and also found that if there -- and we didn't publish the beta-lactamase part of it, but you can test beta-

lactamase on less than you can culture in the supernatant, and it did predict that there would be lower amounts.

The other thing that I think about the variability is that we found that 30 percent of the kids under one on standard doses of amoxicillin and who had what you would expect is the average amount of amoxicillin in the serum had no detectable amoxicillin in the middle ear fluid.

So I think there is also this distribution problem that can occur at times as well.

CHAIRMAN RELLER: Dr. Archer.

DR. ARCHER: I noted from the bacteriology data, if somebody could explain this, that there were actually more H. flu. cultured in this study that there were Strep. pneumo. I think there was 197 H. flu. and 159 Strep. pneumo., which is not the usual distribution.

I was wondering if that could be explained, and then a second question is: how many of the tympanocenteses in acutely ill children yielded no organisms at initial tap?

DR. WYNNE: The two questions, the one is the tap successful growth rate was 70 percent.

DR. ARCHER: How many?

DR. WYNNE: Seventy percent.

And as far as the Haemophilus predominance, slight predominance, two things. One, it probably reflects the fact that one of the sites that enrolled, I think, about 100 of the 521 patients was in Israel where Haemophilus was actually the predominant cause of the pathogen, and many of the Haemophilus came from there, number one.

And, number two, actually looking at other studies in the literature in the last couple of years, it's an increasing percentage of Haemophilus isolate, and I'm not exactly sure that I can explain why, but you see where it used to be in the classic studies of the '80s and '70s. The Streptococcus pneumoniae was almost two to one.

When you look at clinical studies against whether they were done at a single site and they took the samples right down to their own lab or whether they used a central lab like we did, and you have the variance of shipping, they still had Haemophilus influenzae of may 40 percent and Strep. pneumo. of maybe 50 percent of the isolates, and then Moraxella, maybe eight, and the others a few percent.

So really it was pretty -- and we have some slides if we need to that show that that was

pretty consistent with clinical trials of the last several years, and I think the slightly pushover probably reflects the Israeli site.

DR. ARCHER: Is it possible that of the 30 percent that grew no organism, that this was an inability to grow Strep. pneumo. because of the fastidious nature of the organism and so forth?

And did those 30 percent who had negative taps -- how did they behave in terms of therapy?

DR. WYNNE: Two answers. One is I guess that is theoretically true. I would go back, again, to the other studies that we've seen where the eradication or successful growth rates between 65 and 73 percent in the last five years, making it seem very unlikely that our methodologies were vastly different.

Dr. Giebink presented a very careful study that that simply one and of all the others, and according to his data, if anything, we underestimated the Strep. pneumo., which is an organism we actually did well against.

So I don't think it steered the population, and as far as the data you saw in clinical success rates, that only involved the protocol population. Those were only those who grew an organism on initial tympanocentesis.

The other patients that were taken out of the study was an investigational drug. They did not have proven bacteriologic AOM as they were instructed to. Some sites did keep them on.

We had asked them not, but they were not included in the data set of analysis. We have safety data on them. They were included in the ITT safety. They were not included in the clinical evaluation population, but they didn't all complete therapy. So I wouldn't be able to say what happened to them all.

CHAIRMAN RELLER: Dr. Giebink, is this a question for Dr. Wynne?

DR. GIEBINK: It's a comment to the FDA relative to this statement. I think it's a mistake not to follow culture negative patients. Had they been followed, we would have a much better feeling for what this environment was like between end of treatment and the 25, 28-day test of cure.

Absent that information, we really don't know what this population was doing after they finished treatment.

So I would strongly encourage the FDA, as you may consider revising guidelines, to follow these culture negative patients.

CHAIRMAN RELLER: Dr. Murray and then Dr.

Cross.

DR. MURRAY: Yeah, this is for Dr. Craig really, I guess.

Since this was alluded to earlier, we're sort of working on the cusp here with organisms of MIC of four, and the time above MIC predictions based on the thigh model, I realize they were corroborated by clinical data, but are you worried, Bill, that there may be more of a barrier to getting antibiotics into the middle ear? The protein concentrations with inflammation may then be higher. The free drug may be less. So you're going a little bit further, and when you're working with an MIC at the cusp, which could be accurate plus or minus one dilution by the standard criteria, are we -- I mean, 38, 40, 41 percent free drug?

The five to ten percent, is that in serum or is that the percent -- might you not see more in the inflammatory middle ear process?

DR. CRAIG: First of all, acute otitis media is not just an infection inside fluid. It involves a mucosa, concentrations in those kinds of tissues from a variety of techniques have shown to show much more correlation with what one sees in serum for free drug levels.

Furthermore, when we're looking at times above MIC, we're forced with penicillin resistant strains to use neutropenic animals in order for the organism to grown.

When one does look at the effect of white cells on it, this adds an additional factor. So that I feel comfortable using the 35 to 40 percent based on neutropenic because I suspect that it's even lower in the situation with white cells and probably explains why they still got reasonably good bacteriologic cure even for organisms with MICs of eight.

CHAIRMAN RELLER: Dr. Cross.

DR. CROSS: I'd like to ask either Dr. Giebink or McCracken what is known about the potential effect of antigens can kill bacteria that remain in the middle ear in terms of their ability to maintain an inflammatory response, or conversely, what's known about their clearance from the middle ear as perhaps a way of explaining why the response is high on the on therapy evaluation, and yet in terms of clinical eradication at test of cure it's below 50 percent?

Is there any role for an ongoing inflammatory response?

DR. GIEBINK: Yes. There have been studies with pneumococcal cell wall, isolated cell

wall components in the ear that have been done in our lab, and studies with Haemophilus endotoxin done in other labs.

All of these components, even cytosolic pneumolycin (phonetic) induce an inflammatory response in the ear. Relevant to this discussion of antibiotic effect, just as in the rabbit meningitis model where a dose of a beta-lactamase drug precipitates a large rise in inflammatory cell influx into CSF, the very same identical phenomenon occurs in the chinchilla middle ear model which has been used to study inflammation in otitis media, a dose of penicillin greatly accelerates the inflammatory cell influx and the release of TNF alpha and IL-1 beta.

So there is a lot of inflammation in the middle ear that occurs naturally that is accelerated by beta-lactamase drugs and persists well beyond the clearance of viable organisms.

DR. CROSS: As a follow-up to that then, is there any utility in these instances where there are third taps to actually look at any of the inflammatory mediators?

DR. GIEBINK: You bet there are. The difficulty is getting enough material for cytokine assays that except for a few of the assays don't have

the sensitivity at the low concentrations.

The pro inflammatory cytokine kits do. Some of the others don't

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: I had a question, a couple of questions for Scott.

Do we know anything about chronic otitis media in terms of risk factors? Do we know are there any identifiable features that would allow you to predict which children are going to go on to have prolonged fluid?

And my second question is, and I probably should know this and I don't: are the children with chronic effusions any more susceptible to acute infection on top of that?

DR. GIEBINK: Probably the most careful study in this regard are a couple of recent publications by Kathleen Daly from our group. They're cited in some of the materials here.

The risk factors that was pointed out in one of the slides this morning, the risk factors for DRSP, the risk factors for recurrent AOM, and the risk factors for chronic OME are virtually the same with some minor differences, which one would expect because otitis is a disease continuum, and if you have risk

factors to get you into AOM, they're going to be the same ones as you go down the pipeline.

In terms of AOM risk factors or incidence of in children that have chronic OME, Kathy Daly in her last paper has some information in this regard. There is an increased rate, but it is a very muddled issue because a lot of the chronic OME has not been accurately detected with sensitivity in the recurrent AOM studies.

And I think clinically most pediatricians believe and see in their practices recurrent AOM complicating chronic OME rather routinely, and it's one of the large reasons that antibiotic prophylaxis in chronic OME really doesn't have a very big effect.

CHAIRMAN RELLER: Dr. Archer.

DR. ARCHER: Dr. Craig, I have another question for you, just a theoretical question. Can you use time above MIC predictions to possibly predict duration of therapy required to eradicate bacteria from a place like the middle ear, in addition to dosing interval and such as that?

DR. CRAIG: We think you can, but unfortunately we've not gotten the funding yet to do such a study, but I think that's a very important question because we think there's probably a certain

total time above MIC that's required to complete eradication, and that also would vary depending on the rate of killing by the drug.

So with interest now in using shorter courses of therapy, I think that is clearly an area that needs to be studied.

CHAIRMAN RELLER: Dr. Harrison.

DR. HARRISON: Two comments and then a little question.

One, to get back to the enrichment for H. flu. and the low rate of positive cultures in the study, there's a difference in the design of this study than some of the others in that this didn't take all comers and that patients were allowed to be on drug up to a couple of days before they were enrolled.

And if you look at data from patients who have been recently treated, and we did a study; Colin did one as well; that if you look at patients who have been treated within seven days, the rate of sterile effusions is about 40 percent on average.

So that you would expect to have some that have still got residual from prior treatment. So that's one thing.

And prior treatment does enrich for H. flu., especially the beta-lactamase production if

amoxicillin was the previous drug, which is a very common drug to be used.

And the other thing that I think is important to kind of keep in mind is that the middle ear isn't quite like meningitis. I don't want to disagree with Dr. McCracken. That gets me in a lot of trouble, but I think there is a potential outlet for the drainage, and I think this is what you're getting at with persisting antigen.

It may be more like, although not exactly, the urinary tract where you have an outflow. You get inflammation, and the reason I bring that up is that we still use documentation of sterilization on day three as a way to predict efficacy in drugs for urinary tract infections.

And it seems a more parallel system and perhaps one that is also more parallel because recurrences are very frequent, whereas recurrences with meningitis are not.

We don't expect for drugs to eliminate, you know, the perennial bacterial counts. So you get recurrent urinary tract infections, especially when the anatomy isn't really good, and the plumbing is not good in some of these kids. It's pretty much the same thing.

And so I think that that may be a standard also to think about when we're looking at test of cure versus end of therapy.

CHAIRMAN RELLER: Dr. O'Fallon.

DR. O'FALLON: I thought that Dr. Wynne's presentation was magnificent in terms of summarizing an enormous amount of data very, very rapidly. It was lovely.

But I did have problems both with that and with the materials that were given to us by the sponsor, and it's been true of this dialogue all along. We're talking point estimates, 33 percent, 25 percent, 78 percent, with no reference -- it gives us no reference to how big the same was on which that percentage was calculated.

And in particular, in the comparisons with the comparators, the other antibiotics, there were these wonderful presentations, except I have absolutely no idea how big the samples were on which the comparator's percentages were calculated.

So I would really recommend that anything I'm going to see, I'd like to see confidence intervals. If it's a small sample, the confidence interval is going to be really big. If it's a big sample, you'll get a much more precise estimate and

we'll be able to see how truly comparable those success or failure percentages are between groups. So that's one of the things. I can't interpret what I was seeing just by knowing the success or failure percentages.

The second thing that was bothering me about them was if you look at the packages you'll notice that the success probability goes up; the percentage goes up when you go from the ITT to the PP, the per protocol invariably.

Now, there are a lot of good reasons for getting rid of people when you're trying to go for the per protocol, but that is getting rid of the fast failures. If you take a look, they were getting rid of anywhere from 20 to 50 percent of the people in the ITT, in the intention to treat, were dumped out of the protocol in all of those analyses, and that's a big percentage.

I'd like to know more about why those patients -- I mean, they told us in general, but they look to me like fast failures or compliance problems. Why do people fail to comply? They don't want to get well or they're having some kind of problems? Probably the latter.

And so it's very hard to just -- I think

that the truth is somewhere between the ITT and the per protocol. You can figure one of them as being a pessimistic estimate and the other as being a very optimistic estimate, but the truth lies somewhere in between.

And I was having trouble with, again, those comparisons with the other antibiotics because I don't know whether the percentages we were being shown from the comparators were per protocol or intent to treat.

Now, if I were going to be the devil's advocate, I could say, well, they were showing us the intent to treat, which would be lower, remember, and they're showing there per protocol, which would be higher, and you can make anything look good. Remember how to lie with statistics?

So there are a couple of more pieces of information that are needed because we can really interpret those comparisons.

It's asking a lot because I tried to do it for as many of the numbers as I could in preparing for coming here. I tried to do those confidence intervals.

If you could, it would be very helpful to do a diagram where you show us the confidence

intervals on the comparators so that we could really see how comparable they are.

CHAIRMAN RELLER: Thank you, Dr. O'Fallon, for that critique, and we'll get a response, and I have some follow-up questions that are related thereto for Dr. Wynne.

But first, Dr. Cocchetto.

DR. COCCHETTO: Thanks, Dr. Reller.

We'll comment and try to be helpful in the response.

You appreciate that those graphs were quite complex and have quite a bit of data on them. I think the piece that we can address with respect to Augmentin ES directly is probably the most important component we should start with, and that is to show you the confidence intervals for the bacteriologic outcome and to show you the confidence interval for Augmentin ES on the clinical outcomes. That's our drug in our study.

So why don't we address that at the outset? Dr. Wynne, do you want to walk through those?

DR. WYNNE: Sure. Do we have those slides?

Okay. The confidence interval is on the left-hand side. This represents the bacteriologic

success rate overall and for Streptococcus pneumoniae on the left. In the lighter color on the right, which you can barely read, is a 94 percent success eradication. The confidence intervals are easy to read above. That is for the PRP subset.

Next slide.

Confidence intervals for clinical success rates at end of therapy, and based on susceptibility to penicillin. Okay.

DR. O'FALLON: May I make a comment?

Regarding your -- actually, this information can be presented, but rather than bar graphs, you can do it with the confidence interval as a line on a graph as they do in presenting effects of meta analyses, and you can then -- it's very easy to see those visually if you do it that way.

DR. COCCHETTO: I think as Dr. Wynne mentioned, when you look at a number of the other products over the years, the patient populations tend to be somewhat different, and they represent different periods of time.

So while we were looking to illustrate those outcomes for benchmarking purposes, we were somewhat reluctant to go much further than that and put confidence intervals. It could be done, but I

think we've tried to share with you here the confidence intervals for our specific outcomes.

DR. HARRISON: Are those clinical data the per protocol or ITT since she brought that up?

DR. WYNNE: Those clinical data are I would assume to be the ITT for the bacteriology studies, and actually it was the per protocol for the ceftriaxone studies, and it was per protocol for the comparator trials. These were the clinical comparator trials, and they used the per protocol is the first answer.

The second answer is the n's -- I know they have the confidence intervals, and I'm not that quick to do the math. I do remember reviewing the articles themselves in the studies, and the numbers in each subcategory, if you go to a build slide, for instance, are very similar.

The clinical studies where we were presenting the success rate in our Strep. pneumoniae population of 157 patients, their comparator arms are usually around 200 and 220 each.

So when they were shoring overall enrollees' success rates, that was an n of roughly 200 to 220. We're showing an n of 157, 159 Strep. pneumoniae.

I can't do that for confidence intervals, but they're very similar size.

When you went down to the subset studies that they did when they were looking at their S. pneumoniae versus our S. pneumoniae, again, we're still at the 157. Our numbers were usually in the 40s to 50s consistently across the studies because we were following FDA guidance where they asked -- you would get, you know, somewhere around 25 to 50 isolates of each study.

When it got down to the risk factors of those under two in the omnicef study, they had probably 20 patients each. Approximately 46 percent of their enrollees were under age 2. Their Streptococcus pneumoniae population is around 60. So odds are that that was about 20 to 25 age under two.

Going with our 33 per protocol PRSP, there were similar numbers. I don't have confidence intervals.

The only one that there's a big disconnect in number would be the penicillin resistant, and I did allude to that briefly, and I apologize it was so brief. They had nine in their intent to treat, but they evaluated the per protocol, and it was eight in the ceftriaxone study, and they had success at end of

therapy in five of eight and three of eight, at end of therapy in three of eight at test of cure.

A hard jump, but we're trying to present what's the natural history. No one has really evaluated PRSP prospectively like this, and what we could find was one study, and that was what we feel is different. Again, the n's are small.

So those are the numbers without confidence intervals, but they are similar size populations at each time point.

CHAIRMAN RELLER: Dr. Giebink.

DR. GIEBINK: This is very helpful information. What would be even more helpful if we could open that up again. Could you take the cover off the slide projector? Would be seeing the confidence intervals for spontaneous resolution.

And you'll notice that that far right bar had a lower bound of about 22 percent, which is extremely close to the point estimate from the Kaleida study for spontaneous resolution of 20 percent.

So really understanding what the background is against which these are plotted would be helpful, but these alone are tremendously useful information, and just following the lower bounds here as you go down is very important information.

DR. WYNNE: Right, and I would like to note that the 22 percent is also the MIC of eight, and further, that we never expect statistically the tail to wag the dog, and when you're talking about resistant isolates and small n's, the study was designed, as we originally discussed, with 700 enrollees, looking for ten to 14 isolates, amox.-clav. MIC of four, realizing in the discussion with the agency at that time you could not do a statistical study on such a resistant population; also realizing for the slides that Marchant showed earlier, it would take 2,100 patients roughly with taps to show success difference in those PRSP subsets statistically.

I don't know. So those would be an answer to the confidence interval overview. Certainly it's an issue.

CHAIRMAN RELLER: Dr. Wynne, related to these confidence intervals, in the slides preceding this one, I think the numbers in your series 48, 49, and 50 that had the percentages with comparator agents, could we look at one of those where ceftriaxone and other compounds were --

DR. WYNNE: It's the primary series.

CHAIRMAN RELLER: -- were pictorially compared?

DR. WYNNE: Do you know which endpoint was test of cure?

DR. COCCHETTO: Here we are.

DR. WYNNE: Okay.

CHAIRMAN RELLER: Now, the question I have about these and other related slides is could you delineate which, if any of these, were direct comparisons or only presented for a sense of relative efficacy?

And, secondly, what the number of strains, for example, with ceftriaxone were in those studies that had MICs of two, four, eight?

DR. WYNNE: Okay. This particular one is a clinical. So there's two ways to look at that. There's the clinical studies, which were comparator, head-to-head studies that did not involve a baseline bacteriology. Well, then we get to studies with baseline bacteriology.

So I can answer either, whichever you would like me to extrapolate on.

CHAIRMAN RELLER: Well, let's take the clinical studies. Were any of those direct, head-to-head comparisons, or these are compilations from different studies?

DR. WYNNE: We are all direct studies.

The top study was a direct comparison against amox.-clav. Interesting enough, seven to one formulation. It was a comparative per protocol population, an n of about 220 or 230 patients enrolled in each arm. Average was -- no, this is the bacteriology, guys, but this is not a clinical study. The age on that one was four.

The clinical only study -- again, guys, you're talking bacteriology. Can we get those that are clinical only, the follow-up to this, please?

PARTICIPANT: That's 47, 46?

DR. WYNNE: Well, I guess I can answer either again. I was asked to address the clinical comparative studies. That was not a -- right, okay.

Clinical studies. Okay. All right. The seven-to-one study, the 67 percent, and that was a comparative trial. Average age was relatively young. I think it was in the upper end of the age two. It was against four to one, three times a day, amox.-clav. So that data was pulled, and the n was 220-something in each arm, 222 versus 200.

This is zithromax Study 1, was against amox.-clav., and the average age was six. They did not do baseline bacteriology. So that's why it's not presented by pathogen in this slide.

The rocephin Study 1 was a comparison against amox.-clav., and that was a comparative trial, and the baseline bacteriology presented.

The second study, the rocephin Study 2, which is also the TMP-sulfa was the comparison. That was also, again, a comparative trial. The n in that was in the 200s in each arm, mid-twos.

And from what I could surmise, the success rates there were that they used a little higher bar, and they had younger children, age 17.8 months in the rocephin arm and 18 months in the TMP-sulfa arm. Very similar to the population we used for overall.

So the n in all of these studies is essentially the same in the slide, except for the ES PRSP, which of course is going to be a smaller population. It's for protocol 31 with PRSP, but the rest of it are all pathogens, is 383, anyone who grew a bug, or Augmentin ES pneumoniae is 159, and these others are in the low to mid-200s, which if you look at the math needed to do a head-to-head comparison, you can prove noninferiority at about 220 patients per arm, and most were designed as such.

CHAIRMAN RELLER: Dr. O'Fallon, could you comment on these percentages, confidence interval? What numbers are needed to show differences relative

to the astronomical numbers that we had presented to us earlier and with an emphasis on the need for bacteriologic studies to reach reasonable conclusions?

DR. O'FALLON: Well, what they were showing, if you're talking about the Polyanna effect, that's a major problem because at the end where you remember they started out with a big difference in the bacteriologic, and then at the end the clinical was really tight because the differences were so small from effective to noneffective. You'd have to have a huge sample. So that was correct.

You realize that in this package, we haven't seen any truly comparative data. Each of these is treated -- we're just getting descriptions of this data for ES, Augmentin and Augmentin ES, and they are just shown for the effects of the other ones, but we're not being shown comparative data. It's not a comparative study.

So I can't tell, you know. I think the only thing that we can get out of this is to take a look at the confidence intervals, and what they tell us is that there are certain percentage, success or failure percentages that we can rule out that the data are inconsistent with.

So as you were saying, if you looked at

those confidence intervals, they look like they were differences in means, but when you took a look at the lower n, you could see that there were really big differences in the lower bounds of those confidence intervals. In essence, they were ruling out low risk probabilities or low success probabilities, and that's about all we can get with the data we have here, at least as presented to us.

DR. MURRAY: DR. O'Fallon, it would not be a comparator of Augmentin ES, but we do have as overheads the ITT in evaluable assessments done for rocephin with the confidence intervals.

DR. O'FALLON: Yeah.

DR. MURRAY: If one wants that as background information. But, again, the Augmentin that was used was not this. We also have them drawn out at week two for the clinical trials with the bars, but I'm not sure that will answer what you want to see.

DR. O'FALLON: Well, the question, as such, was how big a sample are we going to need to answer certain kinds of questions, and what I'm trying to say is depending on what kind of question you really want to answer and which endpoint you're using, we're going to have to have different sample sizes.

the bacteriological information. Given the descriptive nature of these studies, what numbers of organisms are we talking about where there is bacteriology with MICs of two, four, and eight with the other agents?

Because we have percentages here, and to get a feel for what numbers we're dealing with.

DR. WYNNE: Sure.

CHAIRMAN RELLER: With the confidence interval question.

DR. WYNNE: Okay. Again, in evaluating our PRSP subset, you have a 53 as a percent. That on the n of 33 per protocol, PRSP population.

The next study, the only other study to evaluate directly its PRSP subset was the ceftriaxone study where they have an n of eight. Three of eight were successful at test of cure. It's the same population alluded to just a little bit ago.

The number with an MIC greater than two was not studied. They just reported those at two.

Seeing that this was performed in 1996, I would expect if you look at surveillance studies at that time not a whole lot were greater than two, and they certainly did not do amox.-clav. MICs at that time in the study. So there's no correlation with the

amox.-clav. MIC with that.

There are penicillin resistant two and above, intermediate and susceptible tat.

And looking at the omnicef five-day versus ceftriaxone head to head, that was actually not presented by a pathogen. That was presented as an evaluation of those under two months, I mean -- excuse me -- 24 months of age, those younger than two, where they looked at the success rates. At test of cure they felt really were differentiated around 75 percent if you took all of those patients over two, and then it dropped 250 percent in those under two.

There is not an analysis of Streptococcus pneumoniae by MIC in that study. Why this is added at this time is that's the only other attempt in a study to look at what we would call otitis prone or high risk children because under two is clearly one of the numbers that comes out over and over for a PRSP risk and a recurrent otitis media risk in all of the studies that analyzed either of those risk factors, and that's why that's included in there.

And the n of that, as I surmised earlier, I don't know if I can find it exactly. I probably do have it in some papers. It was in the low 20s. It wasn't three or four or six. It was not 50, 80. It

was a minority.

The enrollment population was 46 percent under the age of two overall.

CHAIRMAN RELLER: If the looked at the amoxicillin-clavulanate, the ceftriaxone numbers there, the 17 of 33 and three of eight, confidence intervals? Do you have a slide showing that?

And also, in the resistant ones, how many were two, four, and eight?

DR. COCCHETTO: I assume that's a question for FDA. That's not our clinical trial.

CHAIRMAN RELLER: Well, but --

DR. COCCHETTO: I'm sorry. Dr. Reller, I assume that question was directed to FDA or committee members as that's not a clinical trial that we sponsored.

CHAIRMAN RELLER: Well, but you showed the data. I mean, clearly an implication of showing those slides is there are differences in efficacy of these compounds and their descriptive maybe not direct comparisons, and I was interested in knowing what the numbers were for the implications of the data presented.

DR. SORETH: Dr. Reller.

CHAIRMAN RELLER: It doesn't make any

difference to me where the information comes from. I just want to know, to have delineated what the limits of interpretability are of the information presented for consideration.

DR. COCCHETTO: Right. No, I appreciate your interest in the trial. We've shared with you as much information as is publicly available to us.

CHAIRMAN RELLER: Dr. Soreth.

DR. SORETH: I think we have an overhead from the Hoffman LaRoche trial looking at outcome by isolates that we'd like to share with you that may shed some light on your question.

CHAIRMAN RELLER: Could we see it?

DR. SORETH: Of course.

DR. MURPHY: We need the overhead set up.

DR. HARRISON: While they're setting up, Dr. O'Fallon, is it reasonable or rational to do confidence intervals on three of eight?

DR. O'FALLON: Yes. I did it, too.

DR. HARRISON: Are you going to have any confidence in the confidence intervals?

DR. O'FALLON: What they show is basically how fragile is the information contained in a sample of size eight. It gives you something.

One of the things it tells you at three

out of eight is it rules out really big responses.

DR. HARRISON: But I'm just saying does the confidence interval add a lot to the sense that eight patients doesn't tell you a lot?

DR. O'FALLON: Well, you'd be surprised at how high that confidence interval is going to go. It's consistent with something like 65 percent. I mean, it goes down to almost zero and up to almost 65 percent, which tells you, gee, this really doesn't tell us a whole lot.

DR. MAKHENE: This is just some of the data from the ceftriaxone study and from the medical officer's review.

Essentially, from that study there were a couple of bacteriologic studies that were done. There were eight isolates that were considered, were classed as penicillin resistant. And of those, at the day 30 visit, three were eradicated out of the total eight.

I actually have in one of my back-up slides -- goes to the breakdown of those patients.

Okay. So from that ceftriaxone study, as I said, there were a couple of bacteriologic studies that were done to specifically look at the issue of bacteriologic efficacy or response for ceftriaxone, and in that study there were a total of eight isolates

that were considered in the class of non-penicillin susceptible.

So there were three out of eight that were considered, as I said, were considered cures, and then in the secondary study -- in the other study there were no isolates at all. I don't know if that helps.

DR. HARRISON: On the PISP versus PRSP, in those?

DR. MAKHENE: Yes.

DR. HARRISON: Were not two of those the intermediates and only one with an MIC greater than two?

DR. MAKHENE: I think it was, but I'd have to go back and check through.

DR. HARRISON: So it was really one of eight if we were comparing the ones with MICs of two or above. I'm just trying to kind of -- and you can't make much out of these data, as Dr. O'Fallon said, but if you didn't present it at all, somebody might worry that you were hiding it.

DR. MAKHENE: Yeah. I have to go and check the specifics of how many were actually PISP and PRSP, but the total was eight, and that eight combined the intermediately susceptible and the fully resistant. It wasn't just fully resistant.

DR. SORETH: Dr. Harrison, as we revisit the review just now, the tally is that of the eight PRSP isolates gotten, five of those eight had an MIC of four, and three of the eight had an MIC of two.

DR. HARRISON: Thanks.

So they really weren't ISP then.

DR. MURPHY: Pardon?

DR. MAKHENE: DR. HARRISON: They weren't really intermediate.

DR. MURPHY: No.

DR. HARRISON: That was just a typo.

CHAIRMAN RELLER: Dr. Murray.

DR. MURRAY: I think the sponsor needs to be congratulated on doing this study for PRSP and have gotten more isolates than other sponsors.

I have a philosophical problem though with lumping them all together, and of course, that's what we're discussing right now. I think if you're a drug like levofloxacin, it's fair to lump PSRP all together, whether the MIC is two, four, eight, or whatever. And so the total number of isolates needs to be low.

But where I see it not be is there are a lot of isolates with an MIC of two and just not enough at four to eight to be able to probably come up with

firm conclusions about anything, and those are probably going to have to be split out in some way philosophically to evaluate this.

And it's maybe a bar that other compounds weren't held to, but they were not in a class whose mechanism directly depended on or were directly related to the mechanism of resistance for PRSP.

So I have a philosophical problem with lumping them all together in a final conclusion when the data are stilted by the MIC of two.

CHAIRMAN RELLER: Dr. Cocchetto.

DR. COCCHETTO: We actually share your concern and certainly explored the data in that way. We've presented some of that.

Dr. Wynne would actually be happy to show you one slice of the data is looking at the data set absent the isolates with an MIC of eight, for example.

Do you want to show that?

DR. MURRAY: But philosophically the twos will still outweigh the fours. So I'm not sure it's fair to lump the fours with the two, much less the eights with the two.

DR. COCCHETTO: You also have the split with twos, fours.

DR. WYNNE: Right. We'll separate out the

answer.

If you look at the proposed breakpoint subset where we designed the study of the breakpoint of up to and including four, if you take away the MICs of eight, what you see in the PRSP subset is a success rate of 93 percent at clinical and at end of therapy, showing that, indeed, does it perhaps have a limit. Yes, and we presented that. Perhaps it's at eight.

But the four, as we see, really no disconnect. There we go. That's -- for those who are color challenged, the left-hand lighter color bar is with the MIC of the isolates, an MIC of eight, included at bacteriologic on therapy and clinical end of therapy results.

If you look to the darker or mildly darker, more purplish color, you see a 97 percent on therapy eradication and a 93 percent clinical success at the end of therapy.

Statistically you're going to see more MICs of two than you are of four certainly. Again, we get back to the program was designed to analyze both those of higher amox.-clav. MICs and those with penicillin resistant Streptococcus pneumoniae, and when you see penicillin resistant Streptococcus pneumoniae, those are MICs above two and above.

And certainly in that group we feel we've shown strong clinical and bacteriologic success.

CHAIRMAN RELLER: Dr. Wynne, could you put up the slide showing two, four, and eight and confidence intervals again?

DR. WYNNE: I don't know if we did two, four, and eight with confidence intervals. We have two -- okay. There were are, two, four and eight, less than two, equal to two, four, and eight. The eight is the far right.

DR. HARRISON: And what's the n?

DR. WYNNE: Well, the n is the bottom. It's 116 less than MIC of two. There's 25, an MIC equal to two. There are four with an MIC equal to four, and there are six with an MIC equal to eight.

CHAIRMAN RELLER: Other questions for this morning's presenters?

(No response.)

CHAIRMAN RELLER: Dr. McCracken, among the points that you emphasized was you thought it was important to study the effect of these different antimicrobials on the nasopharyngeal flora. Could you comment on what is known or not known about the agents under discussion in that regard?

DR. McCRACKEN: Well, actually that was

the study that was supported by SmithKline that I did. I did not know the data. I don't think they're in the book. They were presented at ICCAC last year.

And we compared in an ongoing study in a private practice of pediatrics in which they made the diagnosis of otitis media. We were concerned with the diagnosis of otitis media. We were looking at nasopharyngeal flora before therapy, at ten days or ten to 14 days, at completion of therapy, and two months later.

And with the seven to one currently available preparation, again, Strep. pneumo., it was 100 percent eradicate -- I hate to use the word "eradication" because it may have been suppression -- but disappearance of susceptible of pneumococci, 70 percent against the intermediate, and 30 percent against the resistant strains of Strep. pneumo.

When you looked at the 14 to one preparation, it was 100 percent for the susceptible, 100 percent for the intermediate, 70 percent for the resistant isolates.

Then you go down to two months, and you look at those who had not received antibiotics. Unfortunately half of them had already been treated again with something else, but those who had not,

their flora had returned to their pre-treatment values by and large.

So whatever they had before -- and that's because they went back into day care. These are all high risk, young infants.

CHAIRMAN RELLER: Those differences that you point out, the seven to one, 14 to one preparation, the amount of amoxicillin was --

DR. McCRACKEN: In the seven to one, it's 45 milligrams per kilo a day in two divided doses. In the 14 to one, it's 90 milligrams per kilo a day in two divided doses. So it's 22 and a half per dose versus 45 per dose.

CHAIRMAN RELLER: Right, but given the mechanism of resistance, what would have happened if you had given twice as much of the seven to one preparation? In other words, the amount of amoxicillin was the same, or was that done?

DR. McCRACKEN: Well, essentially that was done, but we didn't raise the clavulanate by doubling the dose of the seven to one preparation. We used the 14 to one that is under consideration here.

CHAIRMAN RELLER: I understand, but the implication is is it the preparation or is it the amount of amoxicillin that's --

DR. McCRACKEN: It's the amount of amoxicillin that's the player here.

CHAIRMAN RELLER: Right. Okay. Dr. Wynne.

DR. WYNNE: I may have not directly addressed what Dr. Murray was questioning because we did not analyze the data in that sense, but I notice that the FDA reviewer did and, indeed, put it in their packet of information. It's on page 13. They demonstrated bacteriologic efficacy on therapy for those by penicillin MICs.

Again, we presented our data as amox.-clav. MICs, and then you're right, lumping the penicillin resistance two and above.

If one looks at the page 13, one sees the intent to treat population at those penicillin MICs equal to two a 22 out of 23 were eradicated. At a penicillin MIC of four, 16 of 18. I think pretty similar. I don't know of confidence intervals. So, again, I'm afraid off the top of my head I can't imagine that they're going to be anything but pretty wide for both since the n's are low.

And then, again, if you look at the per protocol, it's again a pretty similar success rate. Again, I don't have confidence intervals, but that may

have been -- if the concern was the PRSP type claim, then it's only good up to two. I think this evidence shows that the penicillin resistance with MICs of four also had strong bacteriologic eradication.

I'm not sure if that was -- because the data we were presenting here was the amox.-clav. MICs.

CHAIRMAN RELLER: Dr. Harrison?

DR. HARRISON: I just wanted to reflect on your question about doubling the dose of the seven to one compound in that it does get the amoxicillin concentration up to the desired does, but if you double the dose of the clavulanic acid, you will end up with a lot more people not being compliant because the diarrhea rate will more than double, probably triple, and so that's what makes that not an easy thing to do and why the current practice is to supplement with just an extra prescription of amoxicillin to the clavulanic acid, just so that people understood why you wouldn't design a trial that would double the dose of the seven to one.

CHAIRMAN RELLER: No, I understand that, which leads to the question for Dr. Giebink. Why not just more amoxicillin? I mean, how would that work?

And the issue becomes one could conceive of, with the suppression or eradication, if

Haemophilus influenzae or beta-lactamase production was a key issue, this is as regards -- not talking about Haemophilus influenzae efficacy and rates of resistance, but as regards Streptococcus pneumoniae, the mechanism of resistance has come up earlier. The effect, if any, of clavulanic acid on penicillin by altered penicillin binding proteins.

Are there any data looking in a comparative way or even noncomparative way with efficacy rates similar to those in a descriptive way that have been presented here with simply giving more amoxicillin?

DR. GIEBINK: So let me make sure, Barth, I understand. The two questions are, one, can you just increase the dose of amoxicillin, and, two, does clavulanate have any pneumococcal effect.

CHAIRMAN RELLER: Correct.

DR. GIEBINK: On the second point, the only time I've ever heard anybody comment on a clavulanate effect with pneumococcus is a talk that Alex Tomasz gave several years ago, and he alluded to some work in his lab looking at the clavulanate effect on pneumococci, and he suggested that there might be a small effect, but I've never seen that published.

The sponsor may have some information

because I think he may have been doing some of that work with SmithKline.

On the amoxicillin dosing effect, there are two factors there. One, in Dr. McCracken's study that he did, and I think it's 466 that was presented here, and a study that we did published also in Peds. I.D. Journal around the same time as your study where we used, as I recall, a single 20 per kilo dose during treatment. We found linear relationships between dose and concentration in the middle ear fluid.

And as you pump up the dose of drug in the middle ear fluid, you achieve greater times over MIC, notwithstanding distribution changes.

The other important element, the third important element here is that pneumococci with extremely high MICs appear to be somewhat less virulent than those with lower MIC, and I'm referring to a study that was just published about six months ago in one of the otolaryngology journals. The one is escaping me. A chinchilla model was used to compare virulence with either two or three different pneumococcal strains of different MIC, and the strain that had the highest MIC -- I believe it was an eight -- had more rapid clearance from the middle ear and less pathology.

And I don't know of any parallel studies in either other animal models or certainly in otitis models.

Did that answer your question?

CHAIRMAN RELLER: Dr. Murray.

Thanks.

DR. MURRAY: I was just going to say that there were some papers presented at ICCAC showing that if you transformed the genes or fragments in to convert a susceptible strain to resistant, that in the first pass through the animal model -- and I don't remember if it was meningitis or what -- they were attenuated, but with subsequent passage they could return to full virulence without change in the penicillin MIC.

So with that adaptation, there may be restoration.

CHAIRMAN RELLER: Yes.

Dr. Ramirez.

DR. RAMIREZ: Yes. I think that the sponsor presented the data, and they mentioned clearly that they don't expect the clavulanate to have any effect on the pneumococci, and they also clearly say that increasing the dose of the beta-lactam component is necessarily for the penicillin resistance.

But they also stated that if we were going to use this product for empiric therapy, then you need to cover the H. flu., and this is what the clavulanic is going to play a role.

This is going to be important where we have -- I know this is one of the questions -- is what is the role of this product for empiric therapy or for known therapy of penicillin resistance because then is the question: do we need the clavulanic or not?

But for the empiric therapy -- and now I was also surprised to see the amount of H. flu., but with Dr. Harrison's comment that you're going to be using this total for the patients that are already failing initial therapy. Then the amount of H. flu. is going to increase. There's going to be even more need for the clavulanic added to the beta-lactam.

That is an interesting combination just because of the possibility of the increased H. flu. But I think that we all agreed that there's going to be no activity. If we were to know that the patient has the pneumococcal resistant to penicillin, there would be no role for the clavulanic acid, if we were to know that this is the problem for the clinician.

CHAIRMAN RELLER: Dr. Wald.

DR. WALD: Just a comment on the virulence

of pneumococci with increased resistance to penicillin. This has been looked at in a number of clinical studies in children with meningitis and pneumonia, with the thought that they might be more virulent, and they showed comparable virulence to susceptible strains. So I wouldn't expect anything different in the ear. I wouldn't expect them to be less virulent.

DR. RAMIREZ: Dr. McCracken.

DR. McCRACKEN: Well, relevant to your question, Barth, about a double dose of amoxicillin for treatment, there was a presentation by Eugene Leibowitz at ICCAC last year looking at 80 milligrams per kilogram a day of amoxicillin in double tap study, and he showed that it was very effective for the penicillin resistant pneumococci in intermediate resistant pneumococci, but failed in 50 percent of the beta-lactamase producing Haemophilus.

Now, you say failed in 50 percent, but 50 percent is the natural clearance rate. So he clearly showed that you have to have clavulanate there to get rid of those beta-lactamase producing Haemophilus. Otherwise it's only a 50 percent clearance, which is the natural rate.

CHAIRMAN RELLER: Dr. Ramirez.

DR. RAMIREZ: A question. Is there any possibility with the data of this study for the clinician to see the risk factors for the child that may be infected with pneumococcal resistance to penicillin?

You get the pneumococcal resistance. You are identified risk factors, but if you don't have any of the risk factors, day care, or prior antibiotic use, how many of these patients without risk factors may be infected with the pneumococcal resistance to penicillin?

My question is we're trying to develop clinical guidelines for use. You have to give some data to the clinician to see if there's any risk factors for resistant pathogens.

Based on this study, how many patients with pneumococcal resistance to penicillin documented infection were having no risk factor for pneumococcal resistance? Do we have these data?

DR. COCCHETTO: Dr. Wald is answering.

My answer is going to be I don't know that answer. If I understand your question correctly, you'd like us to look at the 41 patients that had confirmed PRSP and look at their baseline clinical characteristics to see if they had one or more risk

factors for that.

DR. RAMIREZ: Exactly. Based on your data would it be fair to say to a clinician that if you don't have any one of these risk factors, it's very unlikely that your patient is going to have a penicillin resistant pneumococci.

DR. COCCHETTO: We can certainly do that. I don't have that number at my fingertips, but we can certainly supply that.

DR. MURPHY: I think we have something like that later, if we could wait until the FDA presentation.

DR. RAMIREZ: Okay.

DR. RAMIREZ: We've had a very detailed discussion, much longer than scheduled. That was purposeful because we want to get these issues addressed to save time this afternoon.

We have scheduled right after lunch the open public hearing. We do not have scheduled comments. Therefore, we'll move this item on the agenda to before lunch and ask now if there are any public comments relevant to this discussion that anyone wishes to make.

(No response.)

CHAIRMAN RELLER: Hearing none, we'll

break for lunch, and we had an hour and five minutes scheduled. We can still take that and reconvene promptly at 1:30 and begin the FDA presentation at that time.

(Whereupon, at 12:25 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:32 p.m.)

CHAIRMAN RELLER: Welcome back. We'll now hear the FDA presentation, and that will be initiated by Dr. Mamodikoe Makhene.

DR. MAKHENE: Good afternoon. I'll be presenting the FDA perspective on the application for Augmentin ES for the treatment of acute otitis media.

Next.

To give an overview of the format for the presentation, I'll briefly discuss the formulations and the indications both for the approved formulations and for the proposed formulation.

Then I'll move on to discuss the pivotal studies that were submitted in the application with a focus on the bacteriologic clinical study.

Then next we'll discuss a little bit of information about safety, and particularly from the bac-T study.

Then I'd like to just summarize some of the issue that were raised by the review of this application, and lastly, review the questions that we have for the committee.

Next.

To begin, Augmentin is a combination anti-

infective agent which consists of amoxicillin and clavulanate, which I guess by now everybody has figured out.

There are two approved formulations for pediatric use. The four to one formulation, and this contains 40 milligrams of amoxicillin per ten milligrams of clavulanate and essentially given every eight hourly, and the ratio, again, is based on the amount of clavulanate to -- the amount of amoxicillin to clavulanate.

The second formulation which is approved is the seven to one formulation, which consists of 45 milligrams of amoxicillin per 6.4 milligrams of clavulanate.

Next.

The approved indication for the two formulations, the seven to one and the four to one formulation, as it reads currently, is as follows. These two products are approved for the treatment of acute otitis media caused by beta-lactamase producing strains of Haemophilus influenzae and Moraxella catarrhalis.

Note that they are not currently approved for Streptococcus pneumoniae, including penicillin resistant strains.

Next.

So the proposed formulation is Augmentin ES, which is the 14 to one formulation; has 90 milligrams of amoxicillin per 6.4 milligrams of clavulanate, and this is to be proposed to be dosed every 12 hours.

Next.

The proposed indication as it reads, as it's been proposed by the sponsor, is as follows. Augmentin ES is indicated for the treatment of acute otitis media caused by beta-lactamase producing strains of H. influenzae or M. catarrhalis and Strep. pneumoniae, including penicillin resistant strains, MIC value for penicillin greater than or equal to two micrograms per mL when suspected.

And I'd like to note, and I think one of the panel members has already pointed out that as proposed this would be for impaired treatment.

Next.

So Augmentin 14 to one would be indicated for use in patients that are three months and older, and the recommended dose would be 90 milligrams per kilogram per day every 12 hours. It would not be indicated for patients who weigh 40 kilograms or more.

Next.

Just to give some perspective in terms of what we currently have available in the armamentarium to treat PRSP, there's no anti-infective agent currently approved to treat acute otitis media due to PRSP.

However, levofloxacin, which is a quinoline, is approved to treat community acquired pneumonia in adults when Strep. pneumoniae, including penicillin resistant strains, occurs with causative pathogen.

And just a note, again, because this is a quinoline it's not approved for use in pediatric patients.

So there were three types of studies which were submitted to support the proposed indication and the anti-application, and in somewhat reverse order, I guess, in terms of how we'll discuss them, the bacteriologic study of Augmentin 14 to one, which you've heard something about, and which will be the focus of the discussion.

A clinical study of the 14 to one formulation compared to the seven to one formulation, and then there were some PK/PD information in the form of two studies that were submitted to support the application.

At this time what we'd like to do is I'd like to introduce Dr. He Sun. He's a biopharmaceutist in CDER, Center for Drug Evaluation and Research, who will present the PK information, and then I'll come back to present the clinical information.

DR. HE SUN: Thanks, Dikoe.

My name He Sun. I'm a biopharm. reviewer, and Frank Pelsor is my team leader.

Next page.

There are total two clinical pharmacology studies included in this submission. The studies were 384 (sic) and study 446. Now, in both PK/PD studies, the time above MIC was used as the pharmacodynamic marker, and time above MIC to be greater than 40 percent of dose interval was used for efficacy predictions.

Let's look at both studies one by one. the first study is the study 382. Now, in this study, I want to bring the committee's attention to the two characteristics.

First of all, there's only a total of five patients. The age distributions are from one month to 12 years, and the dose used in study 382 was 45 milligram per kilogram, seven to one ratio formulation.

So from these studies, they do have four concentration time profile for each subtest, and amoxicillin half-life can be determined from the profile, which is 1.2 hours.

Now, from this profile, in order to calculate the time above MIC for the 14 to one formulation, the concentration was doubled. Then from the doubled concentrate, estimate the curve to calculate time above MICs, and the estimated number for TMIC to be 41 percent.

The second study is study 446. Now, in this study we do have more subjects. Total have 19 subjects, although from this 19 only 17 subjects provided concentrations.

And the formulation used was the 14 to one. However, each subject only provide a one plasma concentration and one middle ear flow concentration.

The concentration collected was one, two, or three hours after the dose. So in order to calculate time above MIC, what the sponsor did was to average the concentration from each time point, for one hour, two hour, or three hours plus dose, and extrapolate the concentration profile from three hours to calculate TMICs. They estimate the value to be 38 percent.

Next.

This figure shows the study 446 results. The level depended on is concentration time profile from plasma and this middle ear flow concentration.

Now, here, let me mention this again. The time collected was one patient per plasma sample, and at one, two, or three hours post dose. So there's no concentration time was obtained beyond three hours. Therefore, half-life of 1.2 hours from study 382 was used to calculate this curve, this portion.

Therefore, the TMIC was estimated based on this extrapolated curve.

In addition, we have to pay attention here. The time points at which the rest occurs are patients who are age two or under. Now, if we roughly look at these distributions, it looks like most of the patients who are age two and under seem to have the lower concentrations in this range.

Now, in this middle ear fluid concentration here, it looks like half patients have middle ear fluid concentration up to three hours above MIC of five and another half below five, and the distribution in the retards (phonetic) of patients who are age two or under.

Next.

Then there is comparison of the results from these two studies. So these are studies from doubling the observed concentrations from study 382.

Now, here is the observed sparse data from study 446. Because we only have up to three hours, all we can do is compare the first three hours, the time concentration data.

For the calculated predicted concentration here, we can see here there seems to be a big disagreement from these two concentrations, the concentrations at observed time points of one, two, or three hours.

And also if you look at this way, there's a trend. The profile for this calculated compared to the actual observed also is somehow in disagreement.

Now, if two studies use two different approach for exactly same objective, but they are disagreement with each other, so one of them must be somehow unreliable or both are unreliable.

In addition, I want to bring one attention is the variabilities here, 71 percent, 69 percent, and 56 percent.

Okay. Let's look at the importance of variability, which actually has already been mentioned before in the discussion this morning. Let's see.

Assuming we know exactly what MIC is required to reach a predicted clinical efficacy, let's say 41 percent of 12 hours, which is five hours here, and you can have two data sets, two situations.

In data set one has more variability. Maybe you have, let's see, from 4.3 up to 6.2 hours and with average of 5.13.

In this case it looks like I have one patient, only one patient below five. Another three seems above. So maybe you guess have 75 percent efficacy.

But in your same data sets, if the distribution changes, there's the increase to 43 percent with exactly the same mean values. In this situation, maybe you get a result only one guy being treated by this dose. Another three actually fall below the TMIC requirement. So only 25 percent distribution.

So I wanted to bring attention here as the distribution not only the mean values, but the distribution range and the characteristic of the distribution. For example, is this a log number distribution or is it a number distribution? It's important factors.

So if the inter-subject variability of

TMIC in the population to be treated, for example, here if we see we're interested in the patient who are 82 and under, and the variability is important information in terms of PK/PD for predictions, and if we agree that time above MIC alone at mean values is not sufficient for predicting of efficacy, and also we have noticed there's large variabilities in the data we have seen, then we will get some feel that there's inadequate information in terms of PK/PD in this situation for predicting of clinical efficacies.

This so-called adequate probably have to pay attention to range. One is the characteristic of the distribution. One is the range of the distribution.

Next one.

Okay. Let me summarize the whole picture here. For studies 382, use the formulation is different in the proposal formulation, which is 7.1 here, and on five subjects past the concentration proved it was estimated by doubling the observed concentrations.

And for the second situation in study 446, two use the formulation of 14 to one, but only have one, two, or three hours' concentration were observed from each subject till they have 17 subjects. The

TMIC was determined by extrapolate the concentration time for 442 calculate.

And also this value was 41 percent, 38 percent TMIC, is just on the margin presented before if we use 40 percent as the cutoff markers.

So in conclusion, I think we can get these three pictures here. First of all, the predicted and observed concentration in the two studies somehow are not in agreement. Therefore, at least one of the study result is not so reliable.

Therefore, determine TMICs because those situations are accurate to estimate not only the mean, but also the distribution of TMIC is not available.

So overall in terms of PK/PD measures because we don't have those information, I guess PK/PD information from the current submissions is not available.

Okay. Thanks.

Dikoe.

DR. MAKHENE: So to pick up where we left off, I'll now discuss the clinical study, which was the comparative study, and then go on to talk about the bac-T clinical study of just the Augmentin 14 to one.

Next.

So the first study, which I'll spend a few minutes on before moving on to the other study, was, again, a comparative study. Patients were given either 14 to one or seven to one for a ten-day period, and this was done between December of 1996 and February '97, and the age range, as you can see, went all the way up to 12 years of age.

This was an all comers trial, which was not enriched, and you've heard a description and we've had some discussion about these two types of trials.

There was no tympanocentesis performed in the study either at baseline or at any of the follow-up visits.

Next.

So there was four scheduled study visits or study contacts. Patients were seen at baseline. They were contacted by telephone while they were on therapy, and they had two follow-up visits, day 12 to 14, and a test of cure visit, days 22 through 28, and at any point they could been seen for an interim visit if they were not clinically doing well.

Next.

The primary efficacy endpoint in the clinical study was based on the clinical response. However, this differed between the sponsor and the FDA

in that it was assessed at the end of therapy in the sponsor's analysis and assessed at the test of cure in the FDA analysis.

Next.

To just briefly give you some feel for the demographics in this population, the two groups were essentially comparable in terms of the breakdown by gender, by race, and we can see that the mean age in the study was a little bit over three years of age and approximately 40 percent of the patients in each treatment arm were under two years of age.

Next.

So based on the FDA per protocol population, the clinical response at the test of cure visit was comparable between the two groups and demonstrating equivalence between the two groups.

However, as I mentioned, because there was no tympanocentesis done in the study, we have no information available about -- we have no micro information available about the isolates at baseline and, therefore, can't really, you know, draw any information from these results about the number of patients with PRSP or any of the other acute otitis media pathogens.

Next.

So which leads us to the next study, and that's the bacteriologic study. This was an open label study, non-comparative, multi-center, and there were 21 centers in the U.S. and four foreign sites.

The study was conducted over about seven months in 1999. Patients received Augmentin 14 to one for a ten-day course to treat an episode of acute otitis media.

The age range was up to 48 months of age, and in the study, this was a double tap study in that patients had a tympanocentesis at baseline, and could have a follow-up tap either at the on therapy visit or at the time that they actually failed.

Next.

And we've talked, again, about enrichment strategies that were used to try to garner as many patients with PRSP for this trial. Specifically patients of young age were recruited. Patients who attended day care, those who had failed previous therapy, or those who had been on prophylaxis.

Next.

Again, as in the clinical study, there were four visits that were scheduled, the baseline or preliminary visit, and then patients were seen -- sorry. Again, at this baseline visit a tap was done.

Patients were seen at an on therapy visit at which a tap could be repeated if they had Strep. pneumoniae that had been isolated at baseline, and then they were seen for two follow-up visits and an end term visit if one was needed.

Next.

As far as the taps that were done, to just go over those in a little bit more detail, there was a tap at baseline for all patients who entered the study. The tap was repeated in all patients with Strep. pneumo. if that had been demonstrated at baseline.

They were retapped at the on therapy visit. The rest of the patients with other pathogens at baseline could be retapped either at the on therapy visit or at the time that the investigator felt that they were a clinical failure.

Next.

And just to note, as Dr. Wynne mentioned, patients without a baseline pathogen were withdrawn from the study.

And then going to the primary efficacy endpoint, it was defined as bacteriologic response by both the sponsor and the FDA. However, as we've discussed, as we've heard earlier this morning, there

was a difference in the timing in that this was assessed at the day four to six visit on therapy in the sponsor's analysis.

Whereas in the FDA analysis, this outcome was presumed from the clinical response at the test of cure.

Next.

The secondary endpoints are those listed here, and next.

In terms of the assessment of the primary clinical outcome, again, the difference as in the clinical study in terms of the timing of the assessment, either at end of therapy or a test of cure in the FDA analysis.

Next.

So moving on to some information about the patient population and some of the actual study results, there were 521 patients in the study who received at least one dose of study therapy, and of those 359 had a baseline pathogen. One hundred and fifty-seven had an isolate of Strep. pneumoniae at baseline, and of that population, of those, 41 had PRSP, and these 41 made up the PRSP ITT population, whereas the overall population of patients who had a demonstrated baseline pathogen fell into the ITT

population.

Next.

So when we look at patients who were in the study, including those who ended up with being withdrawn because of a lack of baseline pathogen, in terms of demographics, the mean age, as has already been mentioned, is approximately 18 months of age, and approximately 60 percent of the patients were male, and around 60 percent where white.

Next.

Comparing the two groups in terms of those who had any baseline pathogen versus those who had particularly PRSP show at baseline, we see that in terms of patients who are under 18 months of age, there were twice as many that fell into the group that had PRSP, and approximately one and a half times as many patients in the PRSP group had received prior antibiotics in the previous three months.

In terms of the breakdown by gender and day care, they're approximately even.

Next.

When we examined the baseline presentations of these patients, both again those with baseline pathogen versus those who had, in particular, PRSP, it's essentially the same going across, but when